Worth the wait: effects of age of onset of marijuana use on white matter and impulsivity

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ORIGINAL INVESTIGATION

Worth the wait: effects of age of onset of marijuana use on white matter and impulsivity

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Abstract
Rationale Marijuana (MJ) use continues to rise, and as the perceived risk of using MJ approaches an all-time historic low, initiation of MJ use is occurring at even younger ages. As adolescence is a critical period of neuromaturation, teens and emerging adults are at greater risk for experiencing the negative effects of MJ on the brain. In particular, MJ use has been shown to be associated with alterations in frontal white matter microstructure, which may be related to reports of increased levels of impulsivity in this population.
Objectives The aim of this study was to examine the relationship between age of onset of MJ use, white matter microstructure, and reported impulsivity in chronic, heavy MJ smokers.
Methods Twenty-five MJ smokers and 18 healthy controls underwent diffusion tensor imaging and completed the Barratt Impulsiveness Scale. MJ smokers were also divided into early onset (regular use prior to age 16) and late onset (age 16 or later) groups in order to clarify the impact of age of onset of MJ use on these variables.
Results MJ smokers exhibited significantly reduced fractional anisotropy (FA) relative to controls, as well as higher levels of impulsivity. Earlier MJ onset was also associated with lower levels of FA. Interestingly, within the early onset group, higher impulsivity scores were correlated with lower FA, a relationship that was not observed in the late onset smokers.
Conclusions MJ use is associated with white matter development and reported impulsivity, particularly in early onset smokers.

Keywords Marijuana · Age of onset · White matter · Diffusion tensor imaging · Impulsivity

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Introduction

Numerous studies report impairment in executive function, specifically behavioral response inhibition, in individuals with marijuana use disorders (Pope and Yurgelun-Todd 1996; Bolla et al. 1999; Gruber et al. 2011a); however, current dialogues regarding legalization of marijuana (MJ) and the use of medical MJ have likely reduced concern regarding the potential negative impact of MJ on cognitive processes. Within the USA, MJ remains the most widely used illicit substance, with an estimated 18.1 million past-month users; 80.5 % of current illicit drug users report using marijuana, and 64.3 % report that it is the only drug they use (SAMHSA 2012). In 2012, Colorado and Washington became the first states to legalize MJ without medical constraints; 2012 also brought a record of 18 states with legalized medical MJ (ONDCP 2012). As current deliberations over the legalization of MJ often highlight the benefits of medical MJ, it is perhaps not surprising that the perceived risk of MJ has reached an all-time historic low among the nation's emerging adults; the most recent Monitoring the Future Study reported that fewer than half of high school seniors said they thought regular MJ smoking was harmful (Johnston et al. 2012). Accompanying the increase in MJ use overall, the average age of first use is now significantly lower than in previous years, dropping from

17.8 years to 17. As adolescence is a time of neuromaturation, with increasing evidence that the adolescent brain is more vulnerable to the effects of drugs than the adult brain (Monti et al. 2005), those at the greatest risk for adverse consequences represent a growing population of consumers of MJ (Schneider 2008), posing a serious public health concern.

In addition to findings that suggest alterations in neurocognitive function (Pope and Yurgelun-Todd 1996; Harvey et al. 2007; McHale and Hunt 2008; Solowij and Pesa 2010; Gruber et al. 2011a; Lisdahl and Price 2012) and inhibitory processing (Gruber and Yurgelun-Todd 2005; Tapert et al. 2007; Schweinsburg et al. 2008; Jacobus et al. 2009a; Gruber et al. 2012a) in chronic MJ smokers relative to control participants, several investigations have also reported alterations in frontal white matter microstructure, measured with diffusion tensor imaging (DTI) techniques in adult MJ smokers (Arnone et al. 2008; Ashtari et al. 2009; Bava et al. 2009; Jacobus et al. 2009b; Gruber et al. 2011b). Arnone et al. (2008) reported increased mean diffusivity (MD)/trace in the prefrontal area of the corpus callosum in MJ relative to controls; this trended towards a positive correlation between diffusivity levels and length of use. Similarly, Ashtari et al. (2009) used voxelwise and tractography techniques and reported reduced fractional anisotropy (FA), a measure of directionality and coherence in white matter fibers, and increased trace in frontotemporal regions in MJ smokers relative to nonsmoking controls. Adolescent studies report similar findings; Bava et al. (2009) highlighted decreases in FA in MJ and alcohol-using adolescents relative to controls in both inferior frontal and temporal areas. Jacobus et al. (2009b) reported reduced white matter in MJ-smoking adolescents who were also binge drinkers relative to controls, but who had *higher FA* values relative to pure binge drinkers, suggesting a potential neuroprotective effect of MJ, perhaps due to reducing alcohol-related oxidative stress. Finally, a recent study from our group found significant reductions in frontal FA in chronic MJ smokers relative to control participants, which was positively correlated with age of onset of MJ use (Gruber et al. 2011b). Overall, these studies suggest altered white matter integrity in MJ smokers relative to control participants and underscore the importance of examining the relationship between age of onset of MJ use and white matter measures, as early exposure may result in enduring structural brain changes.

Impulsivity is a complex and multidimensional construct and is well documented in individuals with substance use problems (Brady et al. 1998; Vitaro et al. 1998; Heil et al. 2006). Higher levels of both self-reported impulsivity, as measured by the Barratt Impulsiveness Scale (BIS), and risk taking have previously been reported in some studies of substance abusers (Lejuez et al. 2002; Lejuez et al. 2003; Gruber and Yurgelun-Todd 2005). Further, an impulsive personality style has previously been identified as both a risk factor and predictor of substance abuse and dependence (Guy et al. 1994). Interestingly, few studies thus far have focused on the specific relationship between reported or observed impulsivity and MJ use. Vangsness et al. (2005) examined the role of positive and negative MJ-related expectancies in MJ users and reported that individuals with higher levels of impulsivity held fewer negative expectancies related to MJ and, in turn, used MJ more often than those with lower levels of impulsivity. In a more recent study of delay discounting, a behavioral index of impulsivity, Johnson et al. (2010) reported that MJ-dependent participants demonstrated a trend towards increased delay discounting relative to controls and former MJ smokers. Further, dependent MJ users scored significantly higher than controls on the impulsiveness subscale of the Eysenck Impulsiveness–Venturesomeness–Empathy questionnaire. Taken together with the neuroimaging findings of MJ smokers that report alterations in response inhibition as well as decision making (Gruber and Yurgelun-Todd 2005; Tapert et al. 2007; Schweinsburg et al. 2008; Jacobus et al. 2009a; Gruber et al. 2012a), impulsivity may, in fact, reflect a stable trait in those who smoke MJ relative to those who do not.

DTI studies of substance abusers have revealed that reductions in FA are associated with impulsivity (Lim et al. 2002; Moeller et al. 2005; Gruber et al. 2011b). Lim et al. (2002) reported reductions in frontal FA in cocaine users relative to controls, suggesting cocaine dependence involves disruptions of orbitofrontal connectivity, which is critical for decision making. Moeller et al. (2005) reported reduced FA in both the genu and rostral body of the anterior corpus callosum in cocaine-dependent participants, as well as *increased* BIS scores and errors of impulsivity on a continuous performance task relative to controls. The authors concluded that reductions in white matter coherence were associated with reported and observed impulsivity and are consistent with prior theories regarding frontal cortical involvement in impaired inhibitory control in cocaine dependence. These findings and our own (Gruber et al. 2011b) lend support to the growing hypothesis that substance abuse is related to white matter microstructural changes, which are associated with compromised ability to perform tasks requiring cognitive control and greater difficulty regulating impulse control.

In order to better understand the relationship among MJ use, white matter microstructure, and self-reported impulsivity, we examined data from chronic, heavy MJ smokers and healthy control participants who did not smoke MJ. We hypothesized that relative to control subjects, MJ smokers would have lower white matter fiber tract integrity, as measured by FA, a measure of directionality and coherence/organization of white matter fibers; higher MD, the average of diffusion in multiple directions; and higher levels of reported impulsivity. Further, we predicted that early onset MJ smokers would drive the finding between the non-MJ-smoking controls and MJ smokers, with earlier age of onset associated with higher reported impulsivity and lower white matter organization.

Methods

Participants

Participants were recruited from the Greater Boston Metropolitan area and included 25 chronic, heavy MJ smokers and 18 healthy control participants who did not smoke MJ. All participants were administered the Structured Clinical Interview for DSM-IV, Patient Edition (SCID-P; First et al. 1994) to ensure that no Axis I pathology was present other than MJ use in the smoking group. In addition, to qualify for enrollment, MJ smokers had to have reported smoking a minimum of 2,500 times, used MJ at least 5 out of the last 7 days, tested positive for urinary cannabinoids, and met DSM-IV criteria for MJ abuse or dependence. MJ smokers were also required to abstain from smoking at least 12 h before their study visit in order to ensure that they were not acutely intoxicated at the time of assessment. All participants were required to provide a urine sample upon arrival at the laboratory, and in order to ensure adherence to the 12-h abstinence schedule, MJ participants were led to believe that our researchers could use this sample to detect the last use of MJ within this time frame, a method we have successfully utilized in the past (Gruber et al. 2012a; Gruber et al. 2012b; Gruber et al. 2011a). Participants, however, were excluded from this study if they reported more than 15 lifetime uses of any category of illicit drugs or recreational use of prescription drugs or had a positive urine screen for any drug (excluding MJ for the smoking group). Individuals were also not enrolled if they reported any head injury with loss of consciousness, a history of any neurological disorder, or previous use of psychotropic medications.

Prior to participation, study procedures were explained, and all participants were required to read and sign an informed consent form approved by the McLean Hospital Institutional Review Board, which described the procedures and voluntary nature of the study.

Study design

Marijuana use was assessed using a modified timeline follow-back procedure. Participants provided information regarding history of MJ use, including age of onset, and duration of use (years), as well as current frequency (smokes per week), magnitude (grams per week), and mode of use. Lifetime use was also determined via the SCID-P. In order to explore the potential impact of age of onset on reported impulsivity and white matter alterations, the MJ smokers were further divided into two groups based on age of onset of regular MJ use. For this study, age of "regular" use of MJ was defined as the age at which subjects began using MJ on a routine, expected, and consistent basis and not the age at which they "tried" MJ for the first time. Early onset was defined as regular MJ use prior to age 16 (n=11) while and late onset was defined as first regular MJ use at age 16 or later (n=14).

In order to assess self-reported impulsivity, all participants completed the Barratt Impulsiveness Scale (BIS 11; Patton et al. 1995), which provides subscales for three domains, including attention, motor, and non-planning, as well as a total impulsiveness score. Although the BIS 11 has been considered a gold standard in self-report assessments of impulsivity, recent work has questioned the utility of the original, three-factor model from which scores are derived. In order to compare the validity of the BIS 11 results obtained using the standard three-score reporting method (Patton et al. 1995), we also utilized two alternative scoring methods, the BIS-Brief as described by Steinberg et al. (2013) which provides a condensed, unidimensional representation of self-reported impulsivity, as well as the Reise et al. (2013) model, which provides a two-factor model of cognitive and behavioral impulsivity. Participants also completed several self-report questionnaires in order to ensure that groups were well matched for clinical state at the time of scanning. Briefly, self-report measures included the Profile of Mood States (Pollock et al. 1979), which provides a profile of current mood state for the individual domains of vigor, anger, confusion, tension, and depression, as well as a total mood disturbance score; the Beck Depression Inventory (Beck et al. 1961); and the State-Trait Anxiety Inventory (Spielberger et al. 1983). Further, participants also completed the Positive and Negative Affect Scale (Watson et al. 1988), which provides a score for both positive and negative affect; the Montgomery–Asberg Depression Rating Scale (Montgomery and Asberg 1979); the Hamilton Anxiety Scale (Hamilton 1959); and the Young Mania Rating Scale (Young et al. 1978). In addition, participants completed the four-factor Wechsler Abbreviated Scale of Intelligence, which provides a measure of general intellectual function and yields an estimate of IQ (Wechsler 1999).

Imaging methods

As part of a larger neuroimaging study, participants completed DTI, which was performed on a Siemens Trio whole-body 3-T MRI scanner (Siemens Corporation, Erlangen, Germany) using a 12-channel, phased array head coil. Data was acquired in the axial plane using a diffusion-weighted standard single shot, double spin echo, echo planar protocol with the following parameters: TR/TE=9.3 s/89 ms; matrix=128×128 on a 25.6-cm FOV; slice thickness=2 mm with a gap of 0; and b value= 700 s/mm^2, for a total acquisition time of 8 min and 41 s. Diffusion was measured along 48 noncollinear directions (number of exCitations=1). For each slice, seven images with no diffusion weighting (b=0 s/mm^2) were also acquired.

Image processing and analysis

All processing of the diffusion-weighted images was performed using the FMRIB Software Library (version 4.1.9; http://www.fmrib.ox.ac.uk/fsl). Images were corrected for motion and eddy current to remove nonlinear artifacts and distortion from the datasets by applying affine alignment of each diffusion-weighted image to the first volume of the diffusion data without gradient ($b=0$). A binary mask was generated from $b=0$ image using the Brain Extraction Tool and tensors were fit using the b factor and diffusion direction matrix. Eigenvalues and eigenvectors were calculated for each voxel resulting in diffusion-weighted scalar maps, including whole brain FA and MD. These scalar maps were then aligned to standard space using the steps described for Tract-Based Spatial Statistics (TBSS), also part of the FSL package. Finally, FA and MD values were extracted in the anatomical regions defined by the John Hopkins University White Matter Label Atlas by registering the white matter labels to subject space using the inverse of the transform previously used to register subject data to standard space. In order to assess white matter differences in regions previously examined (Gruber et al. 2011b), we limited our selection of atlas labels to the following bilateral brain regions: genu of the corpus callosum, corona radiata, and internal and external capsule.

Results

As noted in Table 1, participants were well matched and did not differ significantly with regard to age, IQ, days of alcohol use, and socioeconomic status. In order to assess cigarette smoking/nicotine use, all subjects completed the Fagerstrom Test for Nicotine Dependence (FTND), and scores did not differ significantly between the groups (see Table 1). However, as some previous studies have noted a relationship between white matter measures and cigarette smoking (Jacobsen et al. 2007; Paul et al. 2008; Hudkins et al. 2012), we also assessed how many individuals in both of the study groups used cigarettes and completed a chi-square analysis. The chi-square analysis revealed no significant difference in the observed frequency of current cigarette smokers between the control and MJ groups (X^2 (1, N=43)=2.61).

It is of note that regardless of the scoring method used for the BIS 11, MJ smokers had significantly higher self-reported impulsivity scores relative to the healthy control participants (see Table 2). As a result, and in order to remain comparable with previous work, all additional analyses were completed using only those scores derived from the standard three-factor scoring method. Each of the three BIS subscores and the total score reached statistical significance: attention ($t(41)=1.89$, $p=0.03$), motor ($t(41)=1.91$, $p=0.03$), non-planning ($t(41)=1.92$, $p=0.03$), and total impulsivity ($t(41)=2.28$, $p=0.01$) scores (Table 2).

Comparisons of early and late onset smokers revealed no significant differences in patterns of MJ use between the two groups. However, it is of note that early onset smokers smoked slightly more often (smokes/week; 18.76 vs. 15.51) and more than twice as much MJ per week (grams/week; 14.65 vs. 6.66) as late onset smokers (see Table 3).

Analyses of the DTI data which focused on regions we have previously explored (Gruber et al. 2011b) revealed significantly reduced FA in MJ smokers relative to controls in several regions of interest, including the left ($t(41)=2.10$, $p=0.02$) and right genu of the corpus callosum ($t(41)=2.28$, $p=0.01$) and the left internal capsule ($t(41)=1.71$, $p=0.05$). Trends for reduced FA were also observed in the right internal capsule ($t(41)=1.40$, $p=0.09$) as well as the left ($t(41)=1.52$, $p=0.07$) and right ($t(41)=1.53$, $p=0.07$) external capsule. In addition to reduced FA, mean diffusivity (often inversely correlated with FA values) was also significantly *higher* in MJ smokers relative to controls in the genu (left: $t(41)=1.99$, $p=0.03$; right: $t(41)=2.11$, $p=0.02$) (see Table 4). When divided into early and late MJ smokers, no significant differences in FA were noted between the groups. It is of note, however, that correlation analyses of the entire MJ group which examined the association between age of MJ onset and FA revealed that earlier age of onset was related to *lower*

Table 1 Participant demographics

Demographics	Healthy controls	MJ smokers	T test (2-tailed)
N	18 (7 M, 11 F)	25 (18 M, 7 F)	–
Handedness	17R, 1L	24R, 1L	–
Age	23.11±3.51	23.16±5.87	NS
VIQ	127.39±5.84	120.09±17.83	NS
PIQ	117.22±11.49	114.50±9.42	NS
FTND	0.00±0.00	0.39±0.99	NS
Days of alcohol use in past 30	4.61±4.60	7.24±6.20	NS
Hollingshead 4-factor SES index	49.67±10.85	50.04±10.98	NS

VIQ verbal IQ, *PIQ* performance IQ, *FTND* Fagerstrom test for nicotine dependence, *SES* socioeconomic status

Table 2 Barratt Impulsivity Scale (BIS-11) scores

BIS-11 scoring method	Healthy controls	MJ smokers	p (1-tailed)	Effect size (η^2)
Patton				
Attention	14.58±4.42	16.83±3.40	0.033	0.080
Motor	19.90±3.99	22.54±4.80	0.032	0.081
Non-planning	21.14±5.72	24.02±4.10	0.031	0.083
Total	55.76±12.34	63.50±9.87	0.014	0.113
Reise				
Cognitive	11.22±3.67	12.92±2.71	0.044	0.069
Behavioral	11.99±3.09	14.19±3.65	0.022	0.095
Steinberg				
Brief	14.79±4.44	17.01±3.29	0.034	0.079

levels of FA in the left genu ($r(23)=.344$, $p=0.05$) and right genu ($r(23)=.358$, $p=0.04$); see Fig. 1.

In order to explore the possible relationship between reported impulsivity and white matter alterations, we examined correlations between BIS scores and levels of FA within the MJ smokers. Analyses revealed that FA in the right genu was significantly inversely correlated with BIS attention ($r(23)=-0.500$, $p=0.01$) and motor ($r(23)=-0.337$; $p=0.05$), and a trend was noted for BIS total impulsiveness scores ($r(23)=-0.292$; $p=0.08$); lower FA levels were associated with higher levels of impulsivity. Similarly, left genu FA was negatively correlated with BIS attention scores ($r(23)=-0.372$, $p=0.03$). Interestingly, when the MJ-smoking group was separated into those with early vs. late onset, it appeared that these relationships were driven almost exclusively by the early onset smokers, as higher impulsivity scores on *all* BIS subscales were significantly associated with lower FA in both the left and right genu of early onset smokers (see Fig. 2).

Discussion

As hypothesized, we found significantly reduced FA in both left and right genu of the corpus callosum and significantly higher BIS scores for the MJ smokers relative to the non-MJ-smoking control participants. Correlation analyses revealed a significant relationship between the age of MJ onset and FA in both the left and right genu, suggesting that earlier onset of MJ use is associated with lower white matter fiber tract integrity in these brain regions. Further, while BIS scores were inversely correlated with FA in the MJ smokers, with lower levels of FA associated with higher levels of reported impulsivity, this relationship was driven primarily by the early onset smoking group; higher impulsivity scores were significantly associated with lower FA in both the left and right genu of early onset smokers. In the aggregate, these data suggest that a specific relationship exists between FA and behavioral impulsivity in those who begin smoking MJ prior to the age of 16.

Data from the present study are consistent with previous studies of white matter microstructure in MJ smokers (Arnone et al. 2008; Ashtari et al. 2009; Bava et al. 2009; Jacobus et al. 2009a, 2009b), as well as studies that have independently examined impulsivity in substance-abusing populations (Vangsness et al. 2005; Johnson et al. 2010). Specifically, previous studies have reported decreased FA, as well as higher levels of behavioral impulsivity in MJ smokers. Results from a recent study of the effects of MJ use on white matter integrity suggest that impaired axonal connectivity exists in several regions of the corpus callosum in heavy MJ users (Zalesky et al. 2012). In addition, the authors report that age of onset of MJ was a significant factor in determining the severity of microstructural alteration; both radial and axial diffusivity were correlated with age of MJ onset. The relationship noted between altered white matter measures and age of onset may be the result of the development of white matter in the adolescent brain. During these years, age appropriate myelination is represented by progressive increases in FA and decreases in mean diffusivity (Morriss et al. 1999), which occurs in parallel with the process of cognitive development, most notably improvements in executive function. Early exposure to MJ during a vulnerable period of development may therefore result in lasting morphologic changes as evidenced in animal (Cha et al. 2006; Schneider and Koch, 2003) and human (Yucel et al. 2008; Mata et al. 2010) studies.

Recent investigations also lend support to our finding of increased behavioral impulsivity in MJ smokers. Dougherty et al. (2013) reported significantly higher BIS scores in adolescent MJ smokers relative to non-MJ-smoking controls. Further, MJ smokers demonstrated deficits in several neurocognitive domains, including those related to impulse control. Difficulty with inhibition and impulse control are likely to have consequences in the daily lives of MJ smokers, and in

Table 3 MJ use characteristics: early vs late onset

MJ-related variables	Early MJ onset ($n=11$)	Late MJ onset ($n=14$)	T test (2-tailed)
Age of MJ onset	14.46±0.69	17.93±2.13	<0.01
Smoking episodes/week	18.76±9.38	15.51±7.19	NS
Grams/week	14.65±18.97	6.66±5.56	NS
Duration of MJ use (years)	8.82±5.67	5.14±4.42	NS
Urinary THC concentration	405.67±318.36	743.74±1091.07	NS

Table 4 Mean fractional anisotropy and mean diffusivity in MJ smokers and controls

Fractional anisotropy (FA)	Healthy controls	MJ smokers	*T* test (1-tailed)	Effect size (η^2)
Left genu	4.67E-1±0.67E-1	4.23E-1±0.67E-1	0.02	0.097
Right genu	4.77E-1±0.59E1	4.31E-1±0.68E-1	0.01	0.113
Left corona radiata	3.86E-1±0.71E-1	3.65E-1±0.65E-1	NS	–
Right corona radiata	3.86E-1±0.67E-1	3.61E-1±0.64E-1	NS	–
Left internal capsule	4.76E-1±0.70E-1	4.44E-1±0.53E-1	0.05	0.066
Right internal capsule	4.68E-1±0.55E-1	4.43E-1±0.59E-1	0.09	0.045
Left external capsule	3.39E-1±0.43E-1	3.21E-1±0.37E-1	0.07	0.053
Right external capsule	3.38E-1±0.44E-1	3.20E-1±0.32E-1	0.07	0.054
Mean diffusivity (MD)				
Left genu	1.07E-3±0.24E-3	1.22E-3±0.24E-3	0.03	0.088
Right genu	1.08E-3±0.29E-3	1.26E-3±0.26E-3	0.02	0.098
Left corona radiata	8.47E-4±1.30E-4	8.68E-3±1.30E-4	NS	–
Right corona radiata	8.71E-4±1.36E-4	8.68E-3±1.13E-4	NS	–
Left internal capsule	8.72E-4±1.55E-4	8.91E-3±1.40E-4	NS	–
Right internal capsule	8.95E-4±1.45E-4	8.70E-3±1.25E-4	NS	–
Left external capsule	9.04E-4±1.28E-4	9.32E-3±1.31E-4	NS	–
Right external capsule	8.93E-4±1.23E-4	8.91E-3±1.04E-4	NS	–

fact, results of a recent study of MJ-related problems in frequent users revealed that higher trait impulsivity scores predicted a greater number of problems in MJ users, most commonly procrastination and lower energy levels (Day et al. 2013).

While several studies have *independently* investigated white matter alterations and impulsivity, the current study was focused on the specific *association* between alterations in white matter microstructure and impulsivity in MJ smokers, a relationship previously detected in other substance-abusing populations, including cocaine-dependent subjects (Moeller et al. 2005) and methamphetamine abusers (Salo et al. 2009). Further, the current investigation analyzed the impact of age of onset of MJ use on these variables, which revealed that decreased white matter integrity is associated with higher levels of impulsivity, specifically among individuals who initiated MJ use prior to age 16. This specific relationship, noted primarily in the early onset smokers, is perhaps related to the changing distribution of cannabinoid receptors, which occurs throughout the normal trajectory of white matter development during adolescence. Research in both animals and humans has suggested that the developing nervous system contains an abundance of cannabinoid receptors in neural fiber tracts, which diminishes over time and becomes redistributed heterogeneously throughout the adult brain (Romero et al. 1997; Glass et al. 1998). Higher concentrations of cannabinoid receptors in neural fiber tracts during adolescence may therefore represent a period of specific vulnerability to the effects of MJ use on white matter microstructure, which is of particular concern given the importance of frontal regions for the successful completion of tasks requiring cognitive control and inhibition. In a recent study of healthy children aged 7–9, Chaddock-Heyman et al. (2013) found a significant

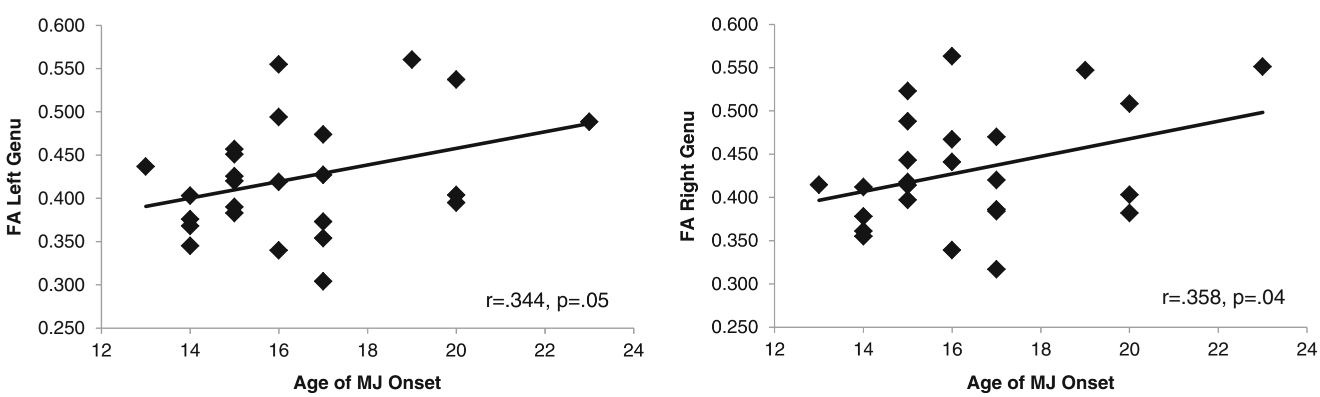

Fig. 1 Correlational analyses of age of onset of MJ use and left and right genu FA

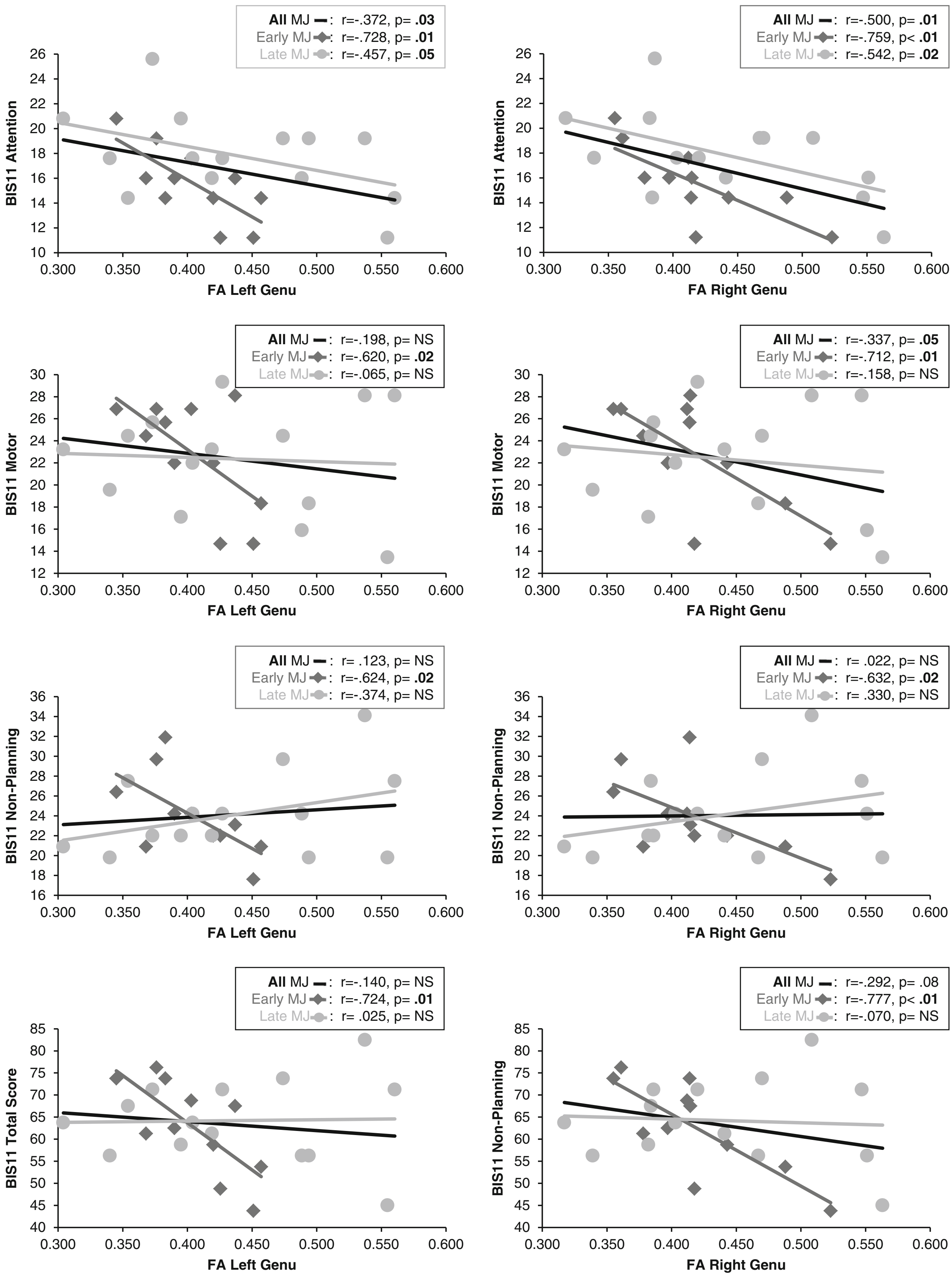

Fig. 2 Correlational analyses of BIS scores vs left and right genu FA

relationship between greater white matter integrity and better performance on trials of a task requiring cognitive control. It is not surprising, therefore, that chronic, heavy MJ smokers, specifically those who began smoking prior to age 16, have been shown to exhibit both white matter alterations and a compromised ability to inhibit inappropriate responses on cognitive measures (Gruber et al. 2012a).

The current finding of higher reported impulsivity scores which are associated with white matter alterations in MJ smokers may also be related to the crossing of fibers through the genu, connecting the left and right dorsolateral prefrontal cortex (DLPFC), which has strong interconnections to the anterior cingulate cortex (ACC; Pandya and Seltzer 1982; Park et al. 2008). Both the ACC and DLPFC are components of the cingulo-fronto-parietal cognitive attention network, which is implicated in executive control, inhibition, attention, and feedback-based decision making (Bush et al. 2008). Decreased FA in the genu of MJ smokers relative to control participants may therefore alter this network, resulting in the difficulties observed in MJ smokers with impulse control. This network may also be particularly susceptible to the effects of long-term exposure of MJ, as the fibers within the genu are thinner than those in other regions, such as the splenium (Aboitiz et al. 1996).

Limitations

While findings from this investigation are compelling, a number of limitations should be noted. The current study included a limited sample size, and future studies should expand research in this area by utilizing larger study samples. Further, in the current study, a few individuals in both the MJ-smoking and healthy comparison group reported having used cigarettes, albeit at extremely low levels. Given the potential impact of cigarette smoking on brain structure, future studies should include only individuals who are naïve to cigarette or nicotine use. It is of note that no significant differences in FTND scores or in the number of individuals who used smoked cigarettes or used nicotine (past or present) were detected between the groups in the current study, making it unlikely that the between differences were impacted by cigarettes or nicotine. However, given the fact that slightly more MJ smokers smoked cigarettes than healthy control subjects (although this difference was not statistically significant), and that recent research has shown *higher* FA in cigarette smokers relative to nonsmokers (Jacobsen et al. 2007; Paul et al. 2008; Hudkins et al. 2012), the inclusion of infrequent cigarette smokers in the currently investigation likely only would have underestimated between group differences in FA.

In addition, previous studies, including our own (Gruber et al. 2011b), have reported frontal white matter alterations in MJ smokers. Although the current study reports decreased FA in MJ smokers and is consistent with our previous work in this area, we previously reported a *positive* correlation between BIS scores and frontal FA. It is of note, however, that the previous investigation included a more limited DTI scheme, acquiring data from only six directions, and only a subset of subjects ($N=10$) had completed both the BIS and DTI measures. In contrast, the present study utilized a more comprehensive DTI acquisition method (48 directions), advanced standardized analytic techniques (TBSS), and a significantly larger sample size, which provides confidence in the current results.

While all of our MJ-smoking participants were classified as chronic, heavy smokers and were required to smoke daily or a minimum of 5 of the last 7 days, *none* of those included in the present study met diagnostic criteria for MJ dependence, while *all* met for MJ abuse. Study findings may therefore be specific to individuals who do not endorse the more negative effects of marijuana use (i.e., psychological issues, inability to stop or cut down on use, withdrawal effects) and to those who do not meet for dependence, despite frequent, heavy use. It is of note, however, that none of the MJ-smoking participants in the current investigation were seeking treatment and would therefore not likely have come to the attention of a health care provider, yet they demonstrated significant differences in measures of white matter organization and impulsivity. Taken together with the growing numbers of emerging adults who smoke MJ and the continually decreasing age of MJ onset, these findings support the need and importance of early identification and intervention among individuals who do not report negative effects of MJ use.

In addition, while we did not find any statistically significant differences between the subject groups on any measure of clinical state or demographic variable, it is possible that the groups differed on measures that we did not assess. While some research has suggested that MJ smokers exhibit differences in personality factors relative to nonsmokers (Terracciano et al. 2008; Berg et al. 2011), which could potentially account for some of the heightened impulsivity observed in MJ smokers, the present sample of MJ smokers exhibited no significant differences in personality measures relative to control participants, as assessed by the NEO five-factor inventory (Costa and McCrae 1992), a well-validated personality inventory that provides scores in several domains, including openness, conscientiousness, agreeableness, extraversion, and neuroticism.

Finally, it remains unclear whether the reductions in FA in MJ smokers noted in the present study are the result of demyelination or damage to white matter, delayed or altered brain developmental patterns in MJ smokers, and if they precede or are the result of MJ use. Further, it is unclear if the alterations noted are reversible after extended periods of abstinence. In the current study, MJ smokers were asked to abstain from MJ use for a minimum of only 12 h in order to ensure they were not acutely intoxicated at the time of scanning. Future investigations should examine individuals with extended abstinence in order to determine what impact this has on measures of white matter microstructure. In addition, studies should also focus on former MJ smokers in order to determine the potential recovery of white matter integrity, as extended abstinence from MJ has been shown to result in a "normalization" of brain function (Sneider et al. 2009).

Conclusions

Findings from this study suggest that chronic, heavy MJ smokers have lower white matter fiber tract integrity relative to non-MJ-smoking participants and that earlier age of MJ onset is associated with lower FA levels. Further, MJ smokers demonstrated higher levels of reported impulsivity relative to control participants, which is related to FA levels, specifically within the early onset MJ group. Notably, lower FA levels are associated with higher reported impulsivity within this sample, suggesting a specific relationship between white matter organization and impulsivity in those individuals who begin smoking MJ prior to age 16. Taken together, these findings reinforce the idea that early onset of MJ use negatively impacts white matter development and is associated with behavioral impulsivity, a combination that may have enduring negative effects, particularly on the developing brain. Data from this study highlight the importance of early identification of MJ use among emerging adults and the need for efforts aimed at delaying or preventing the onset of MJ use.

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Conflicts of interest All authors declare no conflicts of interest.

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